27 October 2003

ROBUST SUMMARY FOR 1,5,9-CYCLODODECATRIENE

Summary

1,5,9-Cyclododecatriene is a liquid with a yellow tint and pungent odor. It has a melting point of -17°C and boiling point of 237°C. 1,5,9-Cyclododecatriene has an autoignition temperature of 244°C, flash point of ca. 88°C, water solubility of 5 mg/L at 20°C, and vapor pressure of 0.09 mm Hg at 20°C.

A vapor pressure of 0.128 mm Hg (25°C) suggests that 1,5,9-cyclododecatriene (CDDT) in the air compartment will exist entirely in the vapor phase. The rate constant for the reaction of CDDT vapor with photochemically generated hydroxyl radicals in the atmosphere is estimated to be $1.7x10^{-10}$ cm^3/molecule-sec at 25°C, which corresponds to a reaction half-life of 0.091 days (24-hour day; $0.5x10^6$ OH/cm^3). The reaction with photochemically generated ozone is estimated to be $6x10^{-16}$ cm^3/molecule-sec at 25°C, corresponding to a half-life of 0.019 days. The combined atmospheric reactions result in an estimated half-life of 0.016 days due to indirect photolytic reactions. The Henry's Law constant for CDDT is estimated to be 0.0281 atm-m^3/mole, and the estimated half-life from a river due to volatilization is 1.3 hours. CDDT is not expected to hydrolyze. Biodegradation is not expected to be an important fate process. Mackay Level III fugacity model, assuming equal emissions to air, water, and soil, predicts that CDDT will occupy mainly the soil, with little occupying water and sediment, and virtually none occupying air. The production and use patterns of the test substance, i.e., approximately 85% of the compound is consumed on-site at the manufacturing plant, suggest that fugitive emission to air may be the highest volume emission route. The short half-life in air due to indirect photolytic reactions and volatility of the test compound indicate there will be little tendency to partition out of air. The measured log Kow for this compound is 4.97 at 25°C. The Bioconcentration Factor (BCF) is estimated as 1339, based on a log Kow measurement of 4.97. However, bioaccumulation is unlikely to be an issue given the relatively high vapor pressure, volatility from water, and likely air emission route.

1,5,9-Cyclododecatriene was moderately toxic to fish, slightly toxic to algae, and moderately or highly toxic to *Daphnia* or shrimp, respectively. Based on measured test concentrations, the following endpoint values have been reported: 96-hour LC_{50} in sheepshead minnows of 2.02 mg/L, 48-hour EC_{50} in *Daphnia* of ca. 5 mg/L, 96-hour LC_{50} in shrimp of 0.47 mg/L, and 4-day EC_{50} in algae of ca. 140 mg/L. Aquatic toxicity estimated by ECOSAR suggests that the compound may be more toxic than observed in actual testing. The available estimated and experimental data indicate that 1,5,9-cyclododecatriene is of medium to high concern for acute toxicity to aquatic organisms. However, the use pattern for the material (primarily a site-limited intermediate) and its high volatility suggest that the potential aquatic exposure is limited and thus the risk to aquatic organisms is also limited.

1,5,9-Cyclododecatriene is slightly toxic via oral and inhalation routes, with an LD_{50} and LC_{50} in rats of 2500 mg/kg and 8.2 mg/L (1230 ppm), respectively. 1,5,9-Cyclododecatriene has a dermal LD_{50} of > 3520 mg/kg. 1,5,9-Cyclododecatriene is a skin and eye irritant. Although the majority of the studies (total of 3) determined that 1,5,9-cyclododecatriene was not a skin sensitizer, one study determined that it was a potent skin sensitizer in animals.

Repeated exposures to 260 ppm of 1,5,9-cyclododecatriene via inhalation produced minimal, reversible effects in the nasal tissue of rats. Histologically, no other evidence of systemic toxicity was observed at this dose level or at 50 ppm. Repeated exposure to 1,5,9-cyclododecatriene produced clinical signs of toxicity (260 ppm) and a decrease in body weights (50 and 260 ppm); however, these changes were reversible. In a repeated dose, developmental/reproductive toxicity screening test, when male rats were dosed with 300 mg/kg 1,5,9-cyclododecatriene via gavage, a test-substance related, biologically significant decrease in body weight gains, accompanied by increased food consumption, and decreased food efficiency was observed. Females administered 100 or 300 mg/kg/day had test substance-related, significantly decreased body weight and body weight gain during gestation that was accompanied by a significant increase in food consumption (300 mg/kg/day only) and significantly decreased food efficiency in 100 and 300 mg/kg/day females. There were no other test substance related effects on clinical observations, neurobehavioral parameters, motor activity, clinical pathology, organ weights, or tissue morphology in males or females at 30, 100, or 300 mg/kg 1,5,9-cyclododecatriene. Body weights of pups in the 300 mg/kg/day group were significantly decreased on lactation days 0 and 4. There were no test substance-related effects on clinical observations, number of pups born, number of pups born alive, number of pups surviving through lactation day 4, or reproductive parameters examined. Based on body weights and/or food consumption the no-observed-adverse-effect levels in this screening test (described above) were 100 mg/kg/day for males, 30 mg/kg/day for females, and 100 mg/kg/day for pups. .

Female rats were exposed to 0, 10, 25, or 67 ppm 1,5,9-cyclododecatriene on gestation days 6-20. Maternal toxicity in the rat, evidenced as decreases in body weight and food consumption, and increase in clinical signs was observed at 67 ppm and 25 ppm 1,5,9-cyclododecatriene. Developmental toxicity was observed only at 67 ppm, as evidenced by a significant reduction in mean fetal weight, and a concomitant increase in the incidence of delayed skeletal ossification. No maternal or developmental toxicity was observed at 10 ppm 1,5,9-cyclododecatriene. The results of this study indicate that 1,5,9-cyclododecatriene is not likely to be uniquely toxic to the rat conceptus.

The compound was negative in the *in vitro* bacterial reverse mutation assay (*Salmonella* and *E. coli*), the *in vitro* clastogenicity study with human lymphocytes, and the *in vivo* rat micronucleus assay.

1,5,9-Cyclododecatriene is manufactured at only one facility, which is located in a rural area in Texas. The majority of the production volume (85%) of the test substance is site limited and used to produce cyclododecane, also a site-limited intermediate, which is used in the production of dodecanedioic acid. The remaining 15% of the production volume is sold to customers who use and consume the substance exclusively as a chemical intermediate. DuPont assesses the capability of a customer using the Product Stewardship System prior to selling a product. The Product Steward works with customers to get an understanding of their application and covers issues pertaining to the use of PPE (personal protective equipment), safety equipment (safety showers, eyewash stations, ventilation needs, etc.), storage concerns, disposal requirements, and any questions concerning the Material Safety Data Sheet.

The single-production facility for the test substance can have as many as 2000 personnel working on-site (construction, contractor, and plant employees), however, the area where the substance is manufactured will have from 2 operators during normal operations up to a total of 60 people during a shutdown or major construction activity. Occupational exposure to 1,5,9-cyclododecatriene is expected to be of low concern when the chemical is handled in accordance with appropriate industrial hygiene and safety measures. Industrial hygiene systems are in place to monitor and assess potential hazards, and implement control measures where needed. The Acceptable Exposure Limit established by DuPont Haskell Laboratory is 2 ppm (13 mg/m^3) (8- and 12-hour TWA), and measured airborne concentrations in the workplace are within the recommended limits. To keep employee exposure below recommended limits, a combination of engineering controls and PPE are required. Adequate safety equipment, such as safety showers, eyewash fountains, and washing facilities are available in the event of an occupational exposure. Individuals handling 1,5,9-cyclododecatriene should avoid contact with eyes, skin, and clothing, thoroughly wash after handling, and avoid breathing any vapors or mist.

Releases to the environment are expected to be minimal under standard operating conditions. Releases to water are negligible, and approximately 1500 lbs. or less are released to the atmosphere on an annual basis. The C12 Unit emissions are well below fenceline limits established by the state of Texas.

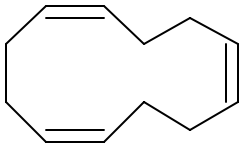
The studies listed below were selected to represent the best available study design and execution for these HPV toxicity endpoints. Other data of equal or lesser quality are not summarized, but are listed as additional references in this document.

1.0 Substance Information

CAS Number: 4904-61-4

Chemical Name: 1,5,9-Cyclododecatriene

Structural Formula:



Other Names: CDDT; CDT

Exposure Limits: 2 ppm (13 mg/m^3), 8- and 12-hour TWA: DuPont Acceptable Exposure Limit (AEL)

10 mg/m^3 (vapor): Maximum Permissible Concentration in Workplace Air (USSR)

2.0 Physical/Chemical Properties

2.1 Melting Point

Value:	-17°C
Decomposition:	No Data
Sublimation:	No Data
Method:	No Data
GLP:	Unknown
Reference:	DuPont Co. (1997). Material Safety Data Sheet No. DU000159 (May 16).
Reliability:	Not assignable because limited study information was available.

Additional References for Melting Point:

Brown, V. K. H. and C. G. Hunter (1968). Br. J. Ind. Med., 25:75-76.

Huels AG (1994). Safety Data Sheet (March 23) (cited in IUCLID (1995). IUCLID Data Sheet "Cyclododeca-1,5,9-triene" (October 23)).

Shell Research Limited (1993). Safety Data Sheet (July 1) (cited in IUCLID

(1995). IUCLID Data Sheet "Cyclododeca-1,5,9-triene" (October 23)).

2.2 Boiling Point

Value:	237°C
Decomposition:	No Data
Pressure:	1013 hPa
Method:	No Data
GLP:	No
Reference:	Huels AG (1994). Safety Data Sheet (23.03.94) (cited in IUCLID (1995). IUCLID Data Sheet "Cyclododeca-1,5,9-triene" (October 23)).
Reliability:	Not assignable because limited study information was available.

Additional References for Boiling Point:

Brown, V. K. H. and C. G. Hunter (1975). Br. J. Ind. Med., 25:75-76.

DuPont Co. (1997). Material Safety Data Sheet No. DU000159 (May 16).

Shell Research Limited (1993). Safety Data Sheet (July 1) (cited in IUCLID (1995). IUCLID Data Sheet "Cyclododeca-1,5,9-triene" (October 23)).

2.3 Density

Value:	0.8906 g/cm^3
Temperature:	20°C
Method:	No Data
GLP:	Unknown
Results:	No Data
Reference:	Brown, V. K. H. and C. G. Hunter (1968). Brit. J. Ind. Med., 25:75-76.
Reliability:	Not assignable because limited study information was available.

Additional References for Density:

DuPont Co. (1997). Material Safety Data Sheet No. DU000159 (May 16).

Huels AG (1994). Safety Data Sheet (March 23) (cited in IUCLID (1995). IUCLID Data Sheet "Cyclododeca-1,5,9-triene" (October 23)).

Shell Research Limited (1993). Safety Data Sheet (July 1) (cited in IUCLID (1995). IUCLID Data Sheet "Cyclododeca-1,5,9-triene" (October 23)).

2.4 Vapor Pressure

Value:	0.12 hPa (0.09 mm Hg)
Temperature:	20°C
Decomposition:	Not Applicable
Method:	Extrapolated from the experimentally determined vapor pressure curve in the source reference: 237.5°C: 760 Torr = 1013 hPa 210.6 400 533 161.8 100 133 119.0 20 26.7 104.0 10 13.3 log (VP) = -2708 * (1/T) + 8.32348 (T in K, VP in hPa)
GLP:	No
Reference:	Huels AG (1994). Safety Data Sheet (March 23) (cited in IUCLID (1995). IUCLID Data Sheet, "Cyclododeca-1,5,9-triene" (October 23)).
Reliability:	Estimated value based on accepted model.

Additional References for Vapor Pressure:

DuPont Co. (1965). Unpublished Data.

DuPont Co. (1997). Material Safety Data Sheet No. DU000159 (May 16).

Shell Research Limited (1993). Safety Data Sheet (July 1) (cited in IUCLID (1995). IUCLID Data Sheet, "Cyclododeca-1,5,9-triene" (October 23)).

2.5 Partition Coefficient (log Kow)

Value:	4.97
Temperature:	25ºC
Method:	The procedure used in the test was based on the recommendations of the following guideline: U.S. EPA Environmental Research Brief EPA/600/S-96/005; August 1995. Four liter glass bottle equilibrium vessels sealed with a ground glass stopper and a teflon stopcock drain located approximately an inch from the bottom of the jar were used for test preparation. Three of these vessels containing water and a magnetic stirring bar were placed on a stirrer at various times and allowed to stir at 25ºC for 24 hours. The first addition of octanol was made and stirring continued for another 24 hours. At the end of this time period, the

remaining octanol containing test substance was added to the vessel. Each vessel was then allowed to slow stir for the appropriate experimental period (24 hours, 3 or 5 days).

Upon completion of the experimental stirring period, the water layer was sampled by stopping stirring, withdrawing a sample, and recording the volume collected. Solvent extraction was then performed using methylene chloride. A 2nd extract was collected and tested in order to confirm quantitative extraction of the CDDT into the methylene chloride. A sample of the octanol phase was obtained and then diluted with methylene chloride.

At the beginning of each day, a standard was run repeatedly until the Gas Liquid Chromatography (GLC) gave a stable, consistent chromatogram. The standards and test samples were injected at consistent time intervals in order to maintain a steady baseline. A solvent blank was run prior to all standard and test sample analyses. Analyses of the standards, to confirm system stability and calibration, coincided with each series of up to 8 test sample injections. All test samples were run in duplicate.

GLP: Yes

Reference: DuPont Co. (2002). Unpublished Data, Haskell Laboratory Report No. DuPont-9818,"n-Octanol/Water Partition coefficient – Slow Stirring Method" (June 17).

Reliability: High because a scientifically defensible or guideline method was used.

Additional References for Partition Coefficient (log Kow):

Eadsforth, C. V. and P. Moser (1983). Chemosphere, 12(11/12):1459-1475.

Huels (1989). Unpublished Data (cited in IUCLID (1995). IUCLID Data Sheet, "Cyclododeca-1,5,9-triene" (October 23)).

IUCLID (1995). IUCLID Data Sheet, "Cyclododeca-1,5,9-triene" (October 23).

McDuffie, B. (1981). Chemosphere, 10:73-83 (ENVIROFATE/116391).

Shell Research Limited (1982). Unpublished Data, Technical Report SBTR.82.042 (cited in IUCLID (1995). IUCLID Data Sheet, "Cyclododeca-1,5,9-triene" (October 23)).

2.6 Water Solubility

Value:	5 mg/L
Temperature:	20°C
pH/pKa:	No Data
Method:	No Data
GLP:	No
Reference:	Huels AG (1994). Safety Data Sheet (March 23) (cited in IUCLID (1995). IUCLID Data Sheet, "Cyclododeca-1,5,9-triene" (October 23)).
Reliability:	Not assignable because limited study information was available.

Additional Reference for Water Solubility:

DuPont Co. (1997). Material Safety Data Sheet No. DU000159 (May 16).

2.7 Flash Point

Value:	ca. 88°C
Method:	Closed cup; method DIN 51755
GLP:	No
Reference:	Huels AG (1994). Safety Data Sheet (March 23) (cited in IUCLID (1995). IUCLID Data Sheet, "Cyclododeca-1,5,9-triene" (October 23)).
Reliability:	Not assignable because limited study information was available.

Additional References for Flash Point:

DuPont Co. (1997). Material Safety Data Sheet No. DU000159 (May 16).

Shell Research Limited (1993). Safety Data Sheet (July 1) (cited in IUCLID (1995). IUCLID Data Sheet, "Cyclododeca-1,5,9-triene" (October 23)).

2.8 Flammability

Results:	Autoignition Temperature = ca. 244°C
Method:	No Data
GLP:	Unknown
Reference:	Huels AG (1994). Safety Data Sheet (March 23) (cited in IUCLID (1995). IUCLID Data Sheet "Cyclododeca-1,5,9-triene" (October 23)).
Reliability:	Not assignable because limited study information was available.

Additional References for Flammability: None Found.

3.0 Environmental Fate

3.1 Photodegradation

Concentration:	No Data
Temperature:	No Data
Direct Photolysis:	Not Applicable
Indirect Photolysis:	If released to the atmosphere, 1,5,9-cyclododecatriene (CDDT) is expected to exist almost entirely in the vapor phase. The rate constant for the reaction of CDDT vapor with photochemically generated hydroxyl radicals in the atmosphere is estimated to be 1.76×10^{-10} cm^3/molecule-sec at 25°C. This value corresponds to a reaction half-life of 0.091 days, assuming an ambient hydroxyl radical concentration of 0.5×10^6 molecules/cm^3 and a 24-hour day. The reaction with photochemically generated ozone (assuming 7×10^{11} mol/cm^3) is estimated to be 6×10^{-16} cm^3/molecule-sec at 25°C, corresponding to a half-life of 0.019 days. The combined effects of the hydroxyl radical and ozone reactions result in an estimated atmospheric half-life of 0.016 days.
Breakdown Products:	No Data
Method:	Calculated by AOP Computer Program, Vers. 1.91, Syracuse Research Corporation. The AOP Program, Version 1.91 from Syracuse Research Corporation, estimates the Atmospheric Oxidation Potential. The AOP program estimates the rate constant for the atmospheric, gas-phase reaction between photochemically produced hydroxyl radicals and organic chemicals. The methodology used by the Atmospheric Oxidation Program is based upon the structure-activity relationship (SAR) methods developed by Dr. Roger Atkinson and coworkers (Atkinson et al., 1987; 1995; 1996; 1984). The AOP Program is described in Meylan and Howard, 1993.
GLP:	No
Reference:	Atkinson, R. et al. (1987). Intern. J. Chem. Kinet., 19:799-828. Atkinson, R. et al. (1995). Atmos. Environ., 29:1685-1695. Atkinson, R. et al. (1996). Environ. Sci. Technol., 30:329-334.

Atkinson, R. et al. (1984). Chem. Rev., 84:437-470.

Meylan, W. M. and P. H. Howard (1993). Chemosphere, 26:2293-2299.

Reliability: Estimated value based on accepted model.

Additional References for Photodegradation: None Found.

3.2 Stability in Water

Concentration: Not Applicable
Half-life: Estimated half-life for a model river is 1.3 hours.
% Hydrolyzed: Not Applicable
Method: The Henry's Law constant for CDDT is estimated to be 0.0281 atm-m^3/mole (Henry v3.10 Program, Group SAR Method in SRC EPIWIN v3.11). Based on this Henry's Law constant, the estimated volatilization half-life from a model river (1 m deep, flowing 1 m/sec, wind velocity of 3 m/sec) is approximately 1.3 hours. The estimated volatilization half-life from a model lake (1 m deep, flowing 0.05 m/sec, wind velocity of 0.5 m/sec) is approximately 123.1 days (EPIWIN v3.11).
GLP: No
Reference: Syracuse Research Corporation EPIWIN v3.11.
Reliability: Estimated value based on accepted model.

Concentration: No data
Half-life: Not expected to hydrolyze.
% Hydrolyzed: No data
Method: Inspection of chemical structure (Harris, 1990).

Modeled. HYDROWIN, v1.67 module of EPIWIN v3.11 (Syracuse Research Corporation). HYDROWIN estimates aqueous hydrolysis rate constants for the following chemical classes: esters, carbamates, epoxides, halomethanes and selected alkyl halides. HYDROWIN estimates acid- and base-catalyzed rate constants; it does NOT estimate neutral hydrolysis rate constants. The prediction methodology was developed for the U.S. Environmental Protection Agency and is outlined in Mill et al., 1987.
GLP: Not Applicable
Reference: Mill, T. et al. (1987). "Environmental Fate and Exposure Studies Development of a PC-SAR for Hydrolysis: Esters, Alkyl Halides and Epoxides," EPA Contract No. 68-02-4254, SRI International, Menlo Park, CA.

Harris, J. C. (1990). Rate of Hydrolysis, Chapter 7, In: Lyman, W. J. et al. (eds.), Handbook of Chemical Property Estimation Methods, American Chemical Society, Washington, DC.

Reliability: Estimated value based on accepted model.

Additional References for Stability in Water: None Found.

3.3 Transport (Fugacity)

Media: Air, Water, Soil, and Sediments

Distributions:

Compartment	% of total distribution[1]	½ life (hours) (advection + reaction)
Air	0.064	0.379
Water	14	360
Soil	70.9	720
Sediment	15	3240

Media: Air Only

Distributions:

Compartment	% of total distribution[2]	½ life (hours) (advection + reaction)
Air	98.2	0.379
Water	0.0775	360
Soil	1.64	720
Sediment	0.083	3240

[1] Based on standard emission scenario:1000 kg/h each for air, water and soil.

[2] Based on air emission scenario: 3000 kg/h to air only.

Adsorption Coefficient: See soil Koc below

Desorption: No Data

Volatility: Henry's Law Constant = 0.0281 atm-m^3/mole (HENRYWIN v3.10, Group method)

Method: Modeled

Inputs:
Molecular Weight: 162.28
Vapor Pressure: 0.128 mm Hg (Huels – calculated at 25°C)
Log Kow: 4.97 (user entered)
Soil Koc: 3.83×10^4 (calculated by model)

Henry's Law Constant - HENRYWIN v3.10 module of EPIWIN v3.11 (Syracuse Research Corporation). Henry's Law Constant (HLC) is estimated by two separate methods that yield two separate estimates. The first method is the bond contribution method and the second is the group

contribution method. The bond contribution method is able to estimate many more types of structures; however, the group method estimate is usually preferred (but not always) when all fragment values are available.

Log Koc – Calculated from log Kow by the Mackay Level III fugacity model incorporated into EPIWIN v3.11 (Syracuse Research Corporation).

Environmental Distribution - Mackay Level III fugacity model, in EPIWIN v3.11 (Syracuse Research Corporation). Emissions (1000 kg/hr) to air, water, and soil compartments.

GLP: Not Applicable

Reference: HENRYWIN –

J. Hine and P. K. Mookerjee (1975). J. Org. Chem., 40(3):292-298.

Meylan, W. and P. H. Howard (1991). Environ. Toxicol. Chem., 10:1283-1293.

Fugacity - The methodology and programming for the Level III fugacity model incorporated into EPIWIN v3.11 (Syracuse Research Corporation) were developed by Dr. Donald MacKay and coworkers and are detailed in:

Mackay, D. (1991). Multimedia Environmental Models: The Fugacity Approach, pp. 67-183, Lewis Publishers, CRC Press.

Mackay, D. et al. (1996). Environ. Toxicol. Chem., 15(9):1618-1626.

Mackay, D. et al. (1996). Environ. Toxicol. Chem., 15(9):1627-1637.

Reliability: Estimated values based on accepted models.

Additional References for Transport (Fugacity):

Data from this additional source support the study results summarized above. This study was not chosen for detailed summarization because the data were not substantially additive to the database.

Karickhoff, S. W. (1981). Chemosphere, 10:833-846 (cited in IUCLID (1995). IUCLID Data Sheet "Cyclododeca-1,5,9-triene" (October 23)).

3.4 Biodegradation

Value:	1% after 28 days
Breakdown Products:	No Data
Method:	The biodegradability of 1,5,9-Cyclododecatriene was tested using the 28-day Closed Bottle test (OECD Guideline 301D). Biodegradation is measured as the loss of dissolved oxygen within the closed test system. A test substance is considered "Readily Biodegradable" if the dissolved oxygen loss at Day 28 is > 60% and this level of biodegradability has been achieved within 14 days after exceeding the 10% level. 1,5,9-Cyclododecatriene reached a peak of 1% biodegradability by Day 28, and therefore is regarded as not "Readily Biodegradable.
GLP:	No
Reference:	DuPont Co. (2000). Unpublished Data, Report No. EMSE-114-00.
Reliability:	High because a scientifically defensible or guideline method was used.

Additional References for Biodegradation:

Data from these additional sources support the study results summarized above. These studies were not chosen for detailed summarization because the data were not substantially additive to the database.

Bridie, A. L. et al. (1979). Water Res., 13(7):627-630 (also cited in TSCA fiche OTS0206201 and OTS0202200).

Huels (n.d.). Unpublished Data (cited in IUCLID (1995). IUCLID Data Sheet, "Cyclododeca-1,5,9-triene" (October 23)).

Shell Oil Co. (1973). TSCA fiche OTS0206200.

3.5 Bioconcentration

Value:	BCF = 1339 (log Kow = 4.97)
Method:	Modeled. BCFWIN v. 2.15 module of EPINWIN v3.11 (Syracuse Research Corporation). BCFWIN estimates the bioconcentration factor (BCF) of an organic compound using the compound's log octanol-water partition coefficient (Kow) with correction factors based on molecular fragments.
GLP:	Not Applicable
Reference:	"Improved Method for Estimating Bioconcentration Factor

(BCF) from Octanol-Water Partition Coefficient," SRC TR-97-006 (2nd Update), July 22, 1997; prepared for Robert S. Boethling, EPA-OPPT, Washington, DC; Contract No. 68-D5-0012; prepared by William M. Meylan, Philip H. Howard, Dallas Aronson, Heather Printup, and Sybil Gouchie; Syracuse Research Corp., Environmental Science Center, 6225 Running Ridge Road, North Syracuse, NY 13212.

Reliability: Estimated value based on accepted model.

Additional Reference for Bioconcentration:

Data from this additional source supports the study results summarized above. This study was not chosen for detailed summarization because the data were not substantially additive to the database.

Chemicals Inspection and Testing Institute (ed.) (1992). Biodegradation and Bioaccumulation Data of Existing Chemicals Based on the CSCL Japan, Japan Chemical Industry Ecology-Toxicology & Information Center, Japan.

Sangster (1989). J. Phys. Chem. Ref. Data, 18:1111-1230.

4.0 Ecotoxicity

4.1 Acute Toxicity to Fish

Type: **96-hour LC_{50}**
Species: *Cyprinodon variegatus* (sheepshead minnow)
Value: 2.02 mg/L (95% confidence interval, 1.69-2.42 mg/L)
Method: Sheepshead minnows were tested in a static bioassay. The definitive test consisted of exposing groups of 20 sheepshead minnows (10 randomly selected organisms for 2 replicates per concentration) to nominal concentrations of 0.3125, 0.625, 1.25, 2.5, or 5.0 mg/L 1,5,9-cyclododecatriene, a dilution water control (Manasquan Inlet control), and a solvent control (2.5 mL/L acetone). Additionally, test concentrations of 10 and 50 mg/L and solvent controls of 5 and 25 mL/L were tested. Observations for biological response and appropriate water quality parameters were made at 24-hour intervals. The organisms were tested for 96 hours under controlled conditions, including a temperature of 22 ± 1°C and a photoperiod of approximately 16 hours of daylight and 8 hours of darkness. Light intensity during the daylight hours was 40-100 fc. Dissolved oxygen (ppm), pH, temperature (°C), conductivity (µmhos/cm), and salinity (ppt) were

	measured in all test chambers at 0, 24, 48, 72, and 96 hours. Alkalinity was determined for each concentration at the beginning and end of the test. The diluent was aerated to maximum oxygen saturation for several hours prior to the preparation of the test solutions. Organisms were not fed during the definitive test. The LC_{50} value was determined using probit analysis.
GLP:	Yes
Test Substance:	1,5,9-Cyclododecatriene, purity 100%
Results:	All dissolved oxygen (DO) values were measured above 60% saturation in all chambers for the 1st 48 hours, and above 40% saturation thereafter, until the end of the test. Temperature was maintained within the prescribed limits of 22 ± 1°C. Conductivity, salinity, and pH were similar between concentrations. Mortality ratios were 0/20, 0/20, 0/20, 0/20, 2/20, 14/20, and 20/20 at 0 (control), 0 (solvent control), 0.3125, 0.625, 1.25, 2.5, and 5.0 mg/L, respectively. All deaths occurred within 24 hours. At 2.5 mg/L, erratic swimming was observed in all organisms shortly after introduction to the test solution. Shortly after introduction in the 5.0 mg/L test concentration all organisms were observed twitching. In the additional 10 mg/L test concentration all organisms were observed twitching within 30 minutes, and were dead within the first hour. In the corresponding solvent control (5.0 mL/L), 10% mortality occurred between 24 and 48 hours. No additional mortality was noted in the remainder of the test period. Therefore, the 10 mg/L test concentration results were determined to be valid for use in an LC_{50} determination. In the additional 50 mg/L concentration, all organisms were observed twitching shortly after introduction to the test solution, and were dead within 30 minutes. However, in the corresponding solvent control (25 mL/L) all organisms were dead within 40 minutes, thus invalidating this test concentration.
Reference:	DuPont Co. (1990). Unpublished Data, Haskell Laboratory Report No. 421-90 (also cited in TSCA fiche OTS0555576).
Reliability:	Medium because a study design was used with nominal concentrations only.
Type:	**96-hour LC_{50}**
Species:	Fish
Value:	0.194 mg/L
Method:	Modeled, using log Kow of 4.97.

GLP:	Not Applicable
Test Substance:	1,5-Cyclooctadiene
Results:	No additional data.
Reference:	Meylan, W. M. and P. H. Howard (1999). User's Guide for the ECOSAR Class Program, Version 0.993 (Mar 99), prepared for J. Vincent Nabholz and Gordon Cas, U.S. Environmental Protection Agency, Office of Pollution Prevention and Toxics, Washington, DC, prepared by Syracuse Research Corp., Environmental Science Center, Syracuse, NY 13210 (submitted for publication).
Reliability:	Estimated value based on accepted model.

Additional References for Acute Toxicity to Fish:

Data from these additional sources support the study results summarized above. These studies were not chosen for detailed summarization because the data were not substantially additive to the database.

Bridie, A. L. et al. (1979). Water Res., 13:623-626.

Huels (1983). Unpublished Data (cited in IUCLID (1995). IUCLID Data Sheet "Cyclododeca-1,5,9-triene" (October 23)).

Shell Research Limited (1982). Unpublished Data, Technical Report SBTR.82.041 (cited in IUCLID (1995). IUCLID Data Sheet "Cyclododeca-1,5,9-triene" (October 23)).

4.2 Acute Toxicity to Invertebrates

Type:	**48-hour EC_{50}**
Species:	*Daphnia magna* (crustacea)
Value:	ca. 5 mg/L
Method:	All test solutions including controls contained 0.5 mL/L of acetone. No compensation was made for volatility such as covering the test vessels. A static system was used, with no renewal of the test solutions. No other data were provided.
GLP:	Yes
Test Substance:	1,5,9-Cyclododecatriene, purity not specified
Results:	The 24-hour EC_{50} was calculated to be 22 mg/L.
Reference:	Shell Research Limited (1982). Unpublished Data, Technical Report SBTR.82.041 (cited in IUCLID (1995). IUCLID Data Sheet "Cyclododeca-1,5,9-triene" (October 23)).
Reliability:	Not assignable because limited study information was available.

Type:	**96-hour LC_{50}**
Species:	*Mysidopsis bahia* (opossum shrimp)
Value:	0.47 mg/L (95% confidence interval, 0.39-0.60 mg/L)
Method:	Opossum shrimp were tested in a static system. The definitive test consisted of exposing groups of 20 opossum shrimp (10 randomly selected organisms for 2 replicates per concentration) to nominal concentrations of 0.0625, 0.125, 0.25, 0.5, or 1.0 mg/L 1,5,9-cyclododecatriene, a dilution water control (Manasquan Inlet control), and a solvent control (5.0 mL/L acetone). Observations for biological response and appropriate water quality parameters were made at 24-hour intervals. The organisms were tested for 96 hours under controlled conditions, including a temperature of 22 ± 1°C and photoperiod of approximately 16 hours of daylight and 8 hours of darkness. Light intensity during the daylight hours was 40-100 fc. Dissolved oxygen (ppm), pH, temperature (°C), conductivity (µmhos/cm), and salinity (ppt) were measured in all test chambers at 0, 24, 48, 72, and 96 hours. Alkalinity was determined for each concentration at the beginning and end of the test. The diluent was aerated to maximum oxygen saturation for several hours prior to the preparation of the test solutions. The mysids were fed a diet of brine shrimp nauplii twice each day for the duration of the test.
GLP:	Yes
Test Substance:	1,5,9-Cyclododecatriene, purity 100%
Results:	All dissolved oxygen (DO) values were measured above 60% saturation in all chambers for the 1st 48 hours, and above 40% saturation thereafter, until the end of the test. Temperature was maintained within the prescribed limits of 22 ± 1°C. Conductivity, salinity, and pH were similar between concentrations. Mortality ratios were 1/20, 0/20, 0/20, 1/20, 0/20, 12/20, and 20/20 at 0 (control), 0 (solvent control), 0.0625, 0.125, 0.25, 0.50, and 1.0 mg/L, respectively. All deaths occurred within 48 hours. Shortly after introduction, twitching was observed in all organisms at 1.0 mg/L.
Reference:	DuPont Co. (1990). Unpublished Data, Haskell Laboratory Report No. 421-90 (also cited in TSCA fiche OTS0555576).
Reliability:	Medium because a study design was used with nominal concentrations only.
Type:	**48-hour EC_{50}**

Species:	*Daphnia*
Value:	0.256 mg/L
Method:	Modeled, using log Kow of 4.97.
GLP:	Not Applicable
Test Substance:	1,5-Cyclooctadiene
Results:	No additional data.
Reference:	Meylan, W. M. and P. H. Howard (1999). User's Guide for the ECOSAR Class Program, Version 0.993 (Mar 99), prepared for J. Vincent Nabholz and Gordon Cas, U.S. Environmental Protection Agency, Office of Pollution Prevention and Toxics, Washington, DC, prepared by Syracuse Research Corp., Environmental Science Center, Syracuse, NY 13210 (submitted for publication).
Reliability:	Estimated value based on accepted model.

Additional Reference for Acute Toxicity to Invertebrates:

Data from this additional source were not summarized because insufficient study information was available.

Huels (1988). Unpublished Data, Report No. D372 (cited in IUCLID (1995). IUCLID Data Sheet "Cyclododeca-1,5,9-triene" (October 23)).

4.3 Acute Toxicity to Aquatic Plants

Type:	**4-day EC_{50}**
Species:	*Selenastrum capricornutum* (algae)
Value:	ca. 140 mg/L
Method:	All test solutions, including controls, contained 0.5 mL/L of acetone. No compensation was made for volatility such as covering the test vessels. A static system was used with no renewal of the test solutions. No other data were provided.
GLP:	Yes
Test Substance:	1,5,9-Cyclododecatriene, purity not specified
Results:	The result was based on the growth rates over the period day 2 to day 4, and was higher than the quoted water solubility of 1,5,9-cyclododecatriene.
Reference:	Shell Research Limited (1982). Unpublished Data, Technical Report SBTR.82.041 (cited in IUCLID (1995). IUCLID Data Sheet, "Cyclododeca-1,5,9-triene" (October 23)).
Reliability:	Not assignable because limited study information was available.

Type:	**96-hour EC_{50}**
Species:	Green algae

Value:	0.190 mg/L
Method:	Modeled, using a log Kow of 4.97.
GLP:	Not Applicable
Test Substance:	1,5-Cyclooctadiene
Results:	The 96-hour ChV was 0.106 mg/L.
Reference:	Meylan, W. M. and P. H. Howard (1999). User's Guide for the ECOSAR Class Program, Version 0.993 (Mar 99), prepared for J. Vincent Nabholz and Gordon Cas, U.S. Environmental Protection Agency, Office of Pollution Prevention and Toxics, Washington, DC; prepared by Syracuse Research Corp., Environmental Science Center, Syracuse, NY 13210 (submitted for publication).
Reliability:	Estimated value based on accepted model.

Additional References for Acute Toxicity to Plants: None Found.

5.0 Mammalian Toxicity

5.1 Acute Toxicity

Type:	**Oral LD_{50}**
Species/Strain:	Male and female rats/Sprague-Dawley
Value:	2.9 mL/kg (2500 mg/kg) (limits of error, 77-129.5%)
Method:	Groups of 5 rats (age not specified) were dosed via oral intubation with 1, 2, 3, 4, or 5 mL/kg 1,5,9-cyclododecatriene (vehicle not specified). The rats were observed for 14 days, then had necropsy and macroscopic examinations performed. The LD_{50} was calculated.
GLP:	No
Test Substance:	1,5,9-Cyclododecatriene, purity not specified
Results:	Mortality of 20, 20, 60, 80, and 100%, was observed at 1, 2, 3, 4, and 5 mL/kg, respectively. Death occurred within 12 hours to 4 days, with the majority of the rats succumbing in 48 hours. Gross necropsy revealed gastrointestinal inflammation (especially of the small intestine), pulmonary congestion, and liver discoloration.
Reference:	Cities Service Research and Development Co. (1961). Unpublished Data, Sample Designation S6-1248; S. A. No. 68862.
Reliability:	Not assignable because limited study information was available.

Additional References for Acute Oral Toxicity:

Data from these additional sources support the study results summarized above. These studies were not chosen for detailed summarization because the data were

not substantially additive to the database.

Muir, C. M. C. (1970). Tunstall card on cyclododecatriene, dated 29/5/1970, Sittingbourne, Shell Research Limited (cited in IUCLID (1995). IUCLID Data Sheet "Cyclododeca-1,5,9-triene" (October 23)).

Shell Research Limited (1970). Unpublished Data (cited in IUCLID (1995). IUCLID Data Sheet "Cyclododeca-1,5,9-triene" (October 23)).

Data from this additional source were not summarized because the study design was not adequate.

Cities Service Research and Development Co. (1961). Unpublished Data, Sample Designation S6-1248; S. A. No. 68862.

Data from this additional source were not summarized because the result was inconsistent with the majority of the other findings.

Huels (1983). Unpublished Data, Report No. 0036 (cited in IUCLID (1995). IUCLID Data Sheet "Cyclododeca-1,5,9-triene" (October 23)).

Type:	**Inhalation LC_{50}**
Species/Strain:	Male rats/Crl:CD
Exposure Time:	6 hours
Value:	8.2 mg/L (1230 ppm) (95% confidence interval, 7.5-8.9 mg/L)
Method:	Rats (10 /group for all exposure levels except 8 and 10 mg/L; 20/group for 8 and 10 mg/L; age not specified) were exposed to 5.0, 6.0, 7.0, 8.0, 8.5, 9.0, or 10.0 mg/L of a 1,5,9-cyclododecatriene aerosol for a 6-hour period. The exposures were conducted under dynamic conditions in a 500 L stainless steel exposure chamber. An aerosol of 1,5,9-cyclododecatriene was generated by delivering a known volume of the liquid material at a constant rate, employing a precision liquid metering pump, into a pressurized atomizing spray nozzle. The resulting aerosol mist was then directed into the main air stream entering the exposure chamber. The mean nominal concentration of aerosol in the chamber was calculated from the rate of liquid delivery and the rate of airflow through the chamber. During exposure, rats were housed individually in wire mesh compartments, centered in the chamber on racks. Observations of the rats for pharmacotoxic signs and time of death were recorded throughout the exposure period.

	Following exposure, surviving rats were housed individually, and observed daily for 14 days. Individual body weights were recorded. Necropsies were performed. The LC_{50} value and 95% confidence interval were estimated statistically.
GLP:	No
Test Substance:	1,5,9-Cyclododecatriene, purity 99.8%
Results:	The mean nominal chamber concentrations were 5.0, 6.0, 7.0, 8.0, 8.5, 9.0, and 10 mg/L for the 5, 6, 7, 8, 8.5, 9, and 10 mg/L concentrations, respectively. Mortality ratios were 0/10, 1/10, 5/10, 5/20, 4/10, 3/10, and 18/20 in the 5, 6, 7, 8, 8.5, 9, and 10 mg/L exposure groups, respectively. Ninety-two percent of the mortality occurred during the actual exposure, as opposed to the 8% latent mortality. The major pharmacotoxic signs observed were gasping (all exposure levels), twitching (all exposure levels), severe muscle spasms (5, 6, 7, 8, 8.5, and 10 mg/L), and tonic convulsions (9 and 10 mg/L). Additional signs of toxicity observed included nasal discharge (all exposure levels), ataxia (9 and 10 mg/L), and depression (5 and 10 mg/L). The severity of the spasm was noticeably increased at the higher levels of chamber concentration. In general, recovery of the rats was complete by the 3rd day following exposure. Major gross findings observed at necropsy of rats that died included distention of all or portions of the gastrointestional tract (6, 7, 8, 8.5, and 10 mg/L) and cyanosis of the exposed body surfaces (6, 7, 8.5, and 10 mg/L). Additional gross findings of rats that died included slight congestion of the lungs (7 and 9 mg/L), liver (7 mg/L), and kidneys (7 and 9 mg/L), and apparent dwarfing of the spleen (8 mg/L). Gross appearance of the organs of the surviving rats of all exposure levels was normal.
Reference:	DuPont Co. (1965). Unpublished Data, Haskell Laboratory Report No. 186-65.
Reliability:	High because a scientifically defensible or guideline method was used.
Type:	**Inhalation Acute Lethal Concentration (ALC)**
Species/Strain:	Male rats/Crl:CD
Exposure Time:	4 hours
Value:	8.1 mg/L (1215 ppm)
Method:	Rats (6/group; approximately 8 weeks old, weighing 242-291 g) were exposed nose-only to either 6.1 or 8.1 mg/L

of 1,5,9-cyclododecatriene atmospheres for a 4-hour period. Test atmospheres were generated by metering measured volumes of 1,5,9-cyclododecatriene into a nebulizer. High pressure air aerosolized the liquid and carried the resulting aerosol/vapor mixture into the exposure chamber. The aerosol portion of the test atmosphere was measured gravimetrically and the vapor phase was measured by gas chromatography. For each exposure, the mean aerosol concentration was added to the mean vapor concentration to calculate the total chamber atmospheric concentration of 1,5,9-cyclododecatriene. Chamber temperature, humidity, airflow, and oxygen concentrations were recorded.

Rats were observed for mortality and clinical signs of toxicity during and immediately following exposure. Because of the dense aerosol generated, all rats could not adequately be observed during the exposures. Observations for clinical signs of toxicity during exposures were limited to "response to stimuli-type" observations. Rats were weighed and observed for clinical signs of toxicity during a 14-day observation period.

GLP: No

Test Substance: 1,5,9-Cyclododecatriene, purity 100%

Results: The aerosols generated in this study were considered to be respirable in rats, as the mass mean median aerodynamic diameters (MMAD) ranged from 2.8 to 2.9 µm. Chamber temperature, relative humidity, airflow, and oxygen concentration were 21-24°C, 36.7-43.6%, approximately 27 L/min, and 21%, respectively.

One rat died during the 8.1 mg/L exposure. No other mortalities were observed during the study. All surviving rats experienced slight to moderate weight losses (3-19% of initial body weight) the day following exposure. These rats subsequently began gaining weight, and did not experience weight loss throughout the remainder of the recovery period. During each exposure, the rats that could be observed exhibited diminished or no response to sound stimulus. Upon removal from the exposure system, surviving rats exhibited ocular discharge (6.1 and 8.1 mg/L), tremors (6.1 and 8.1 mg/L), wet or stained fur (6.1 and 8.1 mg/L), aggressive behavior (8.1 mg/L), vocalization (8.1 mg/L), abnormal gait or mobility (6.1 mg/L), nasal discharge (6.1 mg/L), and irregular respiration (6.1 mg/L). Clinical signs observed during the 14-day observation period included lung noise (8.1 mg/L), vocalization (8.1 mg/L),

	aggressive behavior (8.1 mg/L), irregular respiration (8.1 mg/L), piloerection (8.1 mg/L), ocular or nasal discharge (6.1 and 8.1 mg/L), and stained fur (6.1 and 8.1 mg/L). No clinical signs were observed in either exposure level after day 4 following exposure.
Reference:	DuPont Co. (1996). Unpublished Data, Haskell Laboratory Report No. 318-96 (also cited in TSCA fiche OTS0558489).
Reliability:	High because a scientifically defensible or guideline method was used.

Additional References for Acute Inhalation Toxicity:

Data from this additional source were not summarized because insufficient study information was available.

Cities Service Research and Development Co. (1961). Unpublished Data, Sample Designation S6-1248; S. A. No. 68862.

Data from this additional source were not summarized because the test substance was a mixture or otherwise inappropriate.

DuPont Co. (1966). Unpublished Data, Haskell Laboratory Report No. 114-66 (also cited in TSCA fiche OTS0522190).

Data from this additional source were not summarized because the study design was not adequate.

Gerarde, H. W. (1962). Unpublished Data, Aspiration Hazard and Toxicity of Hydrocarbons and Hydrocarbon Mixtures, Esso Research and Engineering Company.

Type:	**Dermal LD_{50}**
Species/Strain:	Male and female rats/CD
Exposure Time:	24 hours
Value:	> 4 mL/kg (> 3520 mg/kg)
Method:	Two rats of each sex (aged 12-13 weeks) were used at each dose level (2, 3, or 4 mL/kg). The test substance was placed onto the shorn dorso-lumbar skin, and bandaged to contact the skin using an impermeable dressing of aluminum foil and waterproof plaster. The rats were housed individually over the 24-hour exposure period, during which time they were deprived of food, but allowed water *ad libitum*. After 24 hours, the dressings were removed and the exposed area was washed with a tepid dilute detergent solution. The rats were then housed 3/cage, genders separate, and observed for signs of intoxication during the following 9 days (The

	method used was further described in Noakes, D. W. and D. M. Sanderson (1969). Br. J. Ind. Med., 26:59-64).
GLP:	Unknown
Test Substance:	1,5,9-Cyclododecatriene, purity not specified
Results:	None of the rabbits died during the test. All the rats had eschar on their backs when the occlusive dressing had been removed.
Reference:	Shell Research Limited (1976). Unpublished Data, Group Research Report TLGR.0025.76.
Reliability:	Not assignable because limited study information was available.

Additional Reference for Acute Dermal Toxicity:

Data from this additional source support the study results summarized above. This study was not chosen for detailed summarization because the data were not substantially additive to the database.

Cities Service Research and Development Co. (1961). Unpublished Data, Sample Designation S6-1248; S. A. No. 68862.

Type:	**Dermal Irritation**
Species/Strain:	Rabbits/New Zealand White
Method:	The backs of 6 rabbits were closely clipped. One area of the back was abraded and another left intact. The undiluted sample (amount not specified) was applied to the back of each rabbit. The treated areas were covered with plastic shields to keep the material in contact with the skin. Observations were made at various time intervals (intervals not specified). The scoring method of Draize, Woodward, and Calvery (Draize et al. (1944). J. Pharmacol. Expt. Therap., 83:377) was used in evaluating the skin irritating properties of the compound.
GLP:	No
Test Substance:	1,5,9-Cyclododecatriene, purity not specified
Results:	When applied to the intact and abraded skin of rabbits 1,5,9-cyclododecatriene produced minimal erythema in all of the rabbits. In the case of 2 rabbits, minimal edema of the abraded skin was observed in 24 hours. Subsequent observations revealed a gradual return to normal, which was complete after 1 week.
Reference:	Cities Service Research and Development Company (1961). Unpublished Data, Sample Designation S6-1248; S. A. No. 68862.
Reliability:	High because a scientifically defensible or guideline method was used.

Additional References for Dermal Irritation:

Data from these additional sources support the study results summarized above. These studies were not chosen for detailed summarization because the data were not substantially additive to the database.

Huels (1983). Unpublished Study, Report No. 0037 (cited in IUCLID (1995). IUCLID Data Sheet "Cyclododeca-1,5,9-triene" (October 23)).

Shell Research Limited (1976). Unpublished Data, Report No. TLGR.0025.76 (also cited in IUCLID (1995). IUCLID Data Sheet "Cyclododeca-1,5,9-triene" (October 23)).

Shell Research Limited (1983). Unpublished Data, Report SBGR.83.213 (cited in IUCLID (1995). IUCLID Data Sheet "Cyclododeca-1,5,9-triene" (October 23)).

Data from this additional source were not summarized because the result was inconsistent with the majority of the other findings.

Brown, V. K. H. and C. G. Hunter (1968). Br. J. Ind. Med., 25:75-76.

Data from this additional source were not summarized because the focus of the study was skin corrosion potential.

DuPont Co. (1980). Unpublished Data, Haskell Laboratory Report No. 1052-80.

Type:	**Dermal Sensitization**
Species/Strain:	Male guinea pigs/Albino
Method:	Irritation was tested using the undiluted sample and solutions in 1:1 acetone-dioxane containing 13% guinea pig fat (f.a.d.). Initially, applications of 1 drop (ca. 0.05 mL) 1,5,9-cyclododecatriene were lightly rubbed into the intact shaved skin of 12 male albino guinea pigs. In order to determine if the 1-day response might be enhanced by occlusion, 4 additional guinea pigs were exposed on both intact and abraded skin to a minimally irritating concentration. Five hundredths mL of a 10% solution was applied to absorbent non-woven fabric, which was held against the skin with impervious film secured by adhesive. The guinea pigs were then wrapped around the trunk with gauze and elastic bandage. All wrappings were removed the following day. For the sensitization test, guinea pigs treated with uncovered applications, as described above, subsequently received an

	exposure series during a 3-week interval. Six guinea pigs received 9 uncovered applications on abraded skin (10%, 25% x 2, 50%, 25% x 5, in f.a.d) and 6 others received 4 intradermal injections (0.1 mL of 1% solution in dimethyl phthalate). After a 2-week rest period, a challenge test on intact and abraded skin was done, and 12 previously unexposed guinea pigs (controls) were similarly treated.
GLP:	No
Test Substance:	1,5,9-Cyclododecatriene, purity not specified
Results:	1,5,9-Cyclododecatriene was a rapidly acting, strong irritant, but was not a sensitizer of guinea pig skin. On intact skin, the undiluted material produced generally strong erythema with edema through 2 days. Fifty percent, 25%, and 10% solutions in fat-acetone-dioxane produced erythema with dose-related edema during the 1st hour. After 24 hours, the reaction to 50% was slightly less, but that to 25% and 10% solutions had become negligible. On abraded skin, a 50% solution caused strong irritation at 10 minutes, which generally developed into partial necrosis at 1 day. Strong irritation at 10 minutes from a 25% solution diminished slightly by 1 day and markedly by 2 days. At 10%, reaction on abraded skin was not appreciably different from that observed on intact skin. Occluded application of a 10% solution on both intact and abraded skin did not result in significantly increased response.
Reference:	DuPont (1967). Unpublished Data, Haskell Laboratory Report No. 176-67.
Reliability:	High because a scientifically defensible or guideline method was used.
Type:	**Dermal Sensitization**
Species/Strain:	Guinea pigs/Strain not specified
Method:	1,5,9-Cyclododecatriene was injected intradermally or applied to the skin surface in light liquid paraffin at a concentration of 0.1% w/v. The test was carried out by injecting or applying the solution to the shorn skin on the backs of guinea pigs on 3 days in each of 3 successive weeks. The guinea pigs then received no treatment for 10 days, and a challenge dose of the same solution on the right flank and of solvent on the left flank on the 11th day. Following the challenge, the guinea pigs were examined at 1, 24, and 48 hours for signs of a sensitization-type reaction. These methods were described in Hunter et al., 1966 and Brown et al., 1967.
GLP:	No
Test Substance:	1,5,9-Cyclododecatriene, purity >90%

Results:	1,5,9-Cyclododecatriene was found to be a potent skin sensitizer, with 10/10 guinea pigs showing positive sensitive reactions at 24 and 48 hours in both the topical and intradermal tests.
Reference:	Brown, V. K. H. and C. G. Hunter (1968). Br. J. Ind. Med., 25:75-76.
	Hunter, C. G. et al. (1966). Brit. J. Industr. Med., 23:137-141
	Brown, V. K. H. et al. (1967). Ann. Occup. Hyg., 10:123-126.
Reliability:	High because a scientifically defensible or guideline method was used.

Additional References for Dermal Sensitization:

Data from these additional sources support the negative study results summarized above. These studies were not chosen for detailed summarization because the data were not substantially additive to the database.

Huels (1989). Unpublished Data, Report No. 1391 (cited in IUCLID (1995). IUCLID Data Sheet "Cyclododeca-1,5,9-triene" (October 23)).

Shell Research Limited **(**1987). Unpublished Data, Report SBGR.87.175 (cited in IUCLID (1995). IUCLID Data Sheet "Cyclododeca-1,5,9-triene" (October 23)).

Type:	**Eye Irritation**
Species/Strain:	Rabbits/Strain not specified
Method:	Undiluted 1,5,9-cyclododecatriene (0.1 mL) was instilled into the conjunctival sac of the right eye of each rabbit. Observations of the rabbits occurred at 1, 24, 48, and 72 hours, and 1 week following treatment. Fluorescein staining (2% aqueous solution) was used to determine the degree of ocular damage. The scoring method of Draize, Woodward, and Calvery (Draize et al. (1944). J. Pharmacol. Expt. Therap., 83:377) was used in evaluating the eye irritating properties of the test substance.
GLP:	No
Test Substance:	1,5,9-Cyclododecatriene, purity not specified
Results:	Undiluted (0.1 mL) 1,5,9-cyclododecatriene produced erythema of the palpebral conjunctiva, obvious swelling of the lids and nictitating membrane, and lacrimation within 1 hour. Subsequent observations revealed improvement within 24 hours and a return to normal by 1 week. Average numerical evaluation at the end of 1, 24, 48, 72 hours, and

	1 week were 6.6, 2.3, 1.0, 1.0, and 0, respectively, with 110.0 the maximum score attainable.
Reference:	Cities Service Research and Development Company (1961). Unpublished Data, Sample Designation S6-1248; S. A. No. 68862.
Reliability:	High because a scientifically defensible or guideline method was used.

Additional References for Eye Irritation:

Data from these additional sources support the study results summarized above. These studies were not chosen for detailed summarization because the data were not substantially additive to the database.

Brown, V. K. H. and C. G. Hunter (1968). Br. J. Ind. Med., 25:75-76.

Huels (1983). Unpublished Data, Report No. 0038 (cited in IUCLID (1995). IUCLID Data Sheet "Cyclododeca-1,5,9-triene" (October 23)).

5.2 Repeated Dose Toxicity

Type:	**2-Week Inhalation**
Species/Strain:	Rats/Crl:CD®(SD)BR
Sex/Number:	Male/10 per exposure level
Exposure Period:	2 weeks (total of 9 exposures); 2-week recovery period
Frequency of Treatment:	6 hours/day
Exposure Levels:	0, 5, 50, 260 ppm (0, 33, 330, 1700 mg/m^3)
Method:	A total of 8 groups of male rats (2 groups per exposure concentration; approximately 7 weeks old on the day of arrival) were exposed nose-only to vapor or a vapor/aerosol mixture of 1,5,9-cyclododecatriene. All exposure chambers were constructed of stainless steel and glass with a nominal internal volume of 150 L. The chambers were operated in a one-pass, flow-through mode, with air flow rates adequate to provide sufficient oxygen for test rats and enable adequate distribution of 1,5,9-cyclododecatriene in the chambers. For the 5 ppm concentration, vapor atmospheres of 1,5,9-cyclododecatriene were generated by metering the liquid test material into a heated Instatherm flask. Nitrogen was used to carry the 1,5,9-cyclododecatriene vapor to a glass transfer tube where it was mixed with filtered, houseline air and fed into the top of the exposure chamber. Atmospheres of 1,5,9-cyclododecatriene in the 50 and 260 ppm chambers were generated by metering the liquid test material into a nebulizer. Filtered, houseline air

introduced into the nebulizer atomized the liquid test substance and carried the resulting vapor/aerosol mixture into a glass cyclone elutriator. At 50 ppm, the remaining aerosol vaporized in the elutriator, and the vapor was carried into the top of the exposure chamber. The concentration of 1,5,9-cyclododecatriene was controlled by varying the amount of test substance delivered to the flask or nebulizer. The atmosphere concentration of 1,5,9-cyclododecatriene was determined at approximately 60-minute intervals during each exposure by gas chromatography and gravimetric analysis for the vapor and aerosol components, respectively. Chamber airflow, temperature, relative humidity, and oxygen concentrations were recorded.

Four groups of 10 rats per concentration were used for standard toxicological evaluations, and 4 groups of 10 rats per concentration were used for neurotoxicity testing. Individual body weights and clinical signs were recorded. During the exposure, group clinical signs were recorded. In addition, rats were checked for a startle response to an auditory stimulus during exposure. The neurotoxicity groups were given functional observational battery (FOB) assessments (encompassing 34 endpoints) and motor activity (MA) evaluations (encompassing 2 dependent variables) immediately after the 4^{th} and 9^{th} exposures.

Blood was taken from each rat designated for standard toxicology evaluations (10 at the end of the exposure period and 5 at the end of the recovery period). Fifteen hematologic parameters and 17 clinical chemistry parameters were measured or calculated. On the day prior to each bleeding time an overnight urine specimen was collected, and 9 urine chemistry parameters were measured or calculated.

Five rats in each group designated for standard toxicology evaluations were sacrificed and necropsied on test day 12 (day following the last exposure) and test day 26. The liver, kidneys, lungs, testes, and brain were weighed. Each rat was given a complete gross examination, and representative samples of 36 tissues were saved for histopathologic examination. All tissues from the control and 260 ppm groups sacrificed on test day 12 were microscopically examined. Nose, pharynx/larynx, lungs, liver, and kidneys from rats in the 5 and 50 ppm groups at test day 12, and rats in the control and 260 ppm groups at test day 26 were

microscopically examined.

In addition, 6 rats per group designated for neurobehavioral evaluations were evaluated for neuropathology. Six air-exposed control rats were selected as negative controls. After the 9th day, rats were euthanatized followed by whole body perfusion fixation, and 16 tissues were saved. Only tissues from the control and 260 ppm groups were microscopically examined. The remaining neurotoxicity rats were sacrificed without neuropathology evaluations.

GLP: Yes

Test Substance: 1,5,9-Cyclododecatriene, purity 100%

Results: The analytically determined mean concentrations of 1,5,9-cyclododecatriene in the exposure chambers were 5 ± 0.14, 51 ± 1.0, and 260 ± 5.7 ppm for the 5, 50, and 260 ppm exposure levels, respectively. Particle size distribution taken from the 260 ppm chamber during the study showed that the aerosol in the chamber was respirable in rats with mass median aerodynamic diameters (MMAD) of 3.5 or 3.7 µm; 35 or 36% of the particles were less than 3 µm and 98 or 99% of the particles were less than 10 µm. Essentially, no particulates were observed in either the 5 or 50 ppm chambers. The chamber airflow, oxygen concentration, relative humidity, and temperature were 33-35 L/min, 20-21%, 14-30%, and 22-26°C, respectively.

There were no mortalities during the study. Body weights for rats exposed to 5 ppm 1,5,9-cyclododecatriene were similar to those of the control during the entire experiment. Rats exposed to 50 or 260 ppm 1,5,9-cyclododecatriene had significantly lower mean body weights and mean body weight gains when compared to controls. The effects on body weight were reversible.

Diminished or absent startle response to an auditory stimulus was observed in rats exposed to 260 ppm 1,5,9-cyclododecatriene when compared to controls. The response was first observed generally 2 hours into the exposure. Neither onset nor intensity changed over the 9 exposure days, and the rats were responsive prior to the next day of exposure. These effects were not observed in the other exposure groups. Test substance-related clinical signs of toxicity observed immediately after exposure included irregular respiration (260 ppm) and lethargy (260 ppm). Clinical signs of toxicity noted during and after exposure were reversible and were not present in rats prior to the next

exposure.

Body weights measured as part of the functional observational battery assessment were significantly lower for rats in the 260 ppm group when compared to controls. No additional toxicologically relevant findings were observed during the functional observational battery assessments or motor activity evaluation.

There were no test substance-related effects in rats noted during clinical pathology evaluations, and no abnormalities were seen during gross pathology and gross neuropathology examinations. There were no compound-related organ weight effects. Histologic effects attributable to the test substance were found in the nasal tissue of rats in the 260 ppm group. There was a minimal degeneration/necrosis of nasal olfactory epithelium observed immediately after the exposure period. These effects were reversed after the 2-week recovery period. No other test-substance related effects were observed microscopically. There were no test substance-related effects in rats noted during the microscopic neuropathologic evaluation.

References: Bamberger, J. R. et al. (1999). Drug Chem. Toxicol., 22(3):435-454.

DuPont Co. (1996). Unpublished Data, Haskell Laboratory Report No. 857-96 (also cited in TSCA fiche OTS0558489-1).

Kennedy, G. L., Jr. et al. (1998). The Toxicologist, 42:35.

Reliability: High because a scientifically defensible or guideline method was used.

Type: **10-Day Subacute Inhalation**
Species/Strain: Rats/Crl:CD
Sex/Number: Male/20
Exposure Period: 10 days
Frequency of Treatment: 6 hours/day
Exposure Levels: 1.64 mg/L (1/5 the LC_{50}; approximately 250 ppm)
Method: Rats (weighing 230-270 g) were exposed to aerosol concentrations of 1,5,9-cyclododecatriene. The exposures were conducted under dynamic conditions in a 500 L stainless steel exposure chamber. An aerosol of 1,5,9-cyclododecatriene was generated by delivering a known volume of the liquid at a constant rate, employing a

	precision liquid metering pump, into a pressurized atomizing spray nozzle. The resulting aerosol mist was then directed into the main airstream entering the exposure chamber. The mean nominal concentration of aerosol in the chamber was calculated from the rate of liquid delivery and the rate of airflow through the chamber. During exposure, the rats were housed individually in stainless steel wire mesh compartments, positioned alternately each day in the center of the chamber. Observations of the rats for pharmacotoxic signs were recorded at intervals throughout each exposure period. Following each exposure period, rats were housed individually. Individual body weights were recorded. Necropsies were performed, and tissue sections of the lung, liver, spleen, kidneys, bone marrow, and brain were preserved for histopathologic examination.
GLP:	No
Test Substance:	1,5,9-Cyclododecatriene, purity 99.8%
Results:	No deaths occurred throughout the study. In general, no major toxic signs were observed for the rats during exposure. For the most part, a lack of activity was recorded throughout each 6-hour exposure period. Peripheral vasodilatation was apparent throughout the entire study. A slight twitching was noted at the beginning of the exposure period on the 3rd day. The twitching was noted at the beginning of each exposure period for the remaining 7 days, but was noticeably absent as each exposure period progressed. Mean and individual body weight gains appeared normal. No gross tissue alteration of any of the major organs was noted at terminal necropsy. Inhalation of 1,5,9-cyclododecatriene did not produce any distinctive histologic alteration in the brain, lung, liver, or bone marrow of male albino rats. The only possible significant alteration was increased intracytoplasmic granularity of the renal proximal tubule epithelium. Partly because of the nonspecific and somewhat variable appearance of the tubule alteration, the difference was a rather inconsistent degree of the granularity, which was difficult to attribute to the test substance.
Reference:	DuPont Co. (1965). Unpublished Data, Haskell Laboratory Report No. 187-65.
Reliability:	High because a scientifically defensible or guideline method was used.

Type:	**4-Week Gavage**
Species/Strain:	Rat/Crl:CD®(IGS)BR
Sex/Number:	Male and female/10 per sex per dose group
Exposure Period:	Males through test day 55 Females 4 weeks premating through 4-day lactation period
Frequency of Treatment:	Daily
Exposure Levels:	0, 30, 100, 300 mg/kg
Method:	OECD Guideline No. 422.

Male and female rats (approximately 59 and 52 days old at the initiation of dosing, respectively) were administered an oral, daily dose of 0, 30, 100, or 300 mg/kg/day 1,5,9-cyclododecatriene. Females were dosed during a premating period of approximately 4 weeks, a mating period of approximately 1 to 2 weeks, a gestation period of approximately 3 weeks, and a lactation period of approximately 4 days. Females that were not gestating were dosed through the day prior to sacrifice. Males were dosed through test day 55. Body weights, clinical signs, and food consumption for males and females were recorded weekly during the premating period. A clinical pathology evaluation was conducted on all rats after 4 weeks of dosing, and on male rats at the time of scheduled sacrifice. Fourteen hematologic parameters and 18 urine chemistry parameters were measured or calculated. In addition, 13 urinalysis parameters were evaluated. A neurobehavioral test battery, consisting of motor activity (encompassing 2 dependent variables) and functional observational battery assessments (encompassing 34 endpoints), was conducted on all study rats prior to compound administration and following approximately 4 weeks of test substance administration. For males, body weights and clinical signs of toxicity continued to be collected through the last day of dosing on test day 55.

Following the 4-week premating period, each female was paired with a male of the same dosage group during a 1-2 week mating period. Measurements of body weight, food consumption, food efficiency, and clinical signs of toxicity in females were conducted weekly during gestation and on lactation days 0 and 4. At the end of an approximately 3-week post-mating period, surviving males and presumed non-pregnant females were sacrificed, and on lactation day 4, lactating females and offspring were sacrificed. Ten organs were weighed, and 40 tissues were preserved for microscopic examination. The testes,

	epididymides, ovaries, and gross lesions from all high-dose and control group rats were examined microscopically. All other preserved tissues from 5 male and 5 female rats, randomly selected from the high-dose and control groups were examined microscopically. Livers from 5 randomly selected female rats in the 30 and 100 mg/kg/day groups that delivered at least 1 live offspring were also examined microscopically. Offspring were weighed and evaluated for clinical abnormalities. Additional details for reproductive and pup/weanling information can be found in Section 5.4.
GLP:	Yes
Test Substance:	1,5,9-Cyclododecatriene, purity 99.86%
Results:	Analysis of test substance indicated that the test substance was homogeneously distributed at all levels and that the concentrations were at the targeted level. The stability results indicated that the test substance was stable at all concentrations under the conditions of the study. A test-substance related, biologically significant decrease in body weight gains occurred in male rats administered 300 mg/kg/day. Decreased body weight gain in the 300 mg/kg/day males was accompanied by increased food consumption and decreased food efficiency. Females administered 100 or 300 mg/kg/day had test substance-related, significantly decreased body weight and body weight gain during gestation that was accompanied by a significant increase in food consumption (300 mg/kg/day only) and significantly decreased food efficiency in 100 and 300 mg/kg/day females. There were no test substance-related effects on clinical observations in males and females during the premating phase or in females during gestation or lactation. There were no test substance-related effects on reproductive parameters. Additional details for the reproductive toxicity subset can be found in Section 5.4. There were no test substance-related changes in neurobehavioral parameters or motor activity. There were no toxicologically significant changes in hematology, coagulation, clinical chemistry, or urinalysis parameters in males or females. There were no test substance-related, biologically adverse changes in organ weights or tissue morphology in males or females.

	The no-observed-adverse-effect level (NOAEL) was 100 mg/kg/day for males and 30 mg/kg/day for females.
Reference:	DuPont Co. (2000). Unpublished Data, Haskell Laboratory Report No. DuPont-3682.
Reliability:	High because a scientifically defensible or guideline method was used.

Additional References for Repeated Dose Toxicity: None Found.

5.3 Developmental Toxicity

Species/Strain:	Rats/Crl:CD®(SD)BR
Sex/Number:	Female/22 per exposure concentration
Route of Administration:	Inhalation
Exposure Period:	Days 6-20 of gestation; Cesarean section on Day 21
Frequency of Treatment:	6 hours/day
Exposure Levels:	0, 10, 25, 67 ppm
Method:	Female rats were bred by the supplier (Charles River) and were at 1, 2, or 3 days of gestation on the day of arrival. The time-mated female rats were exposed whole-body to generated atmospheres of the test substance in 300 L stainless steel and glass exposure chambers. Atmospheres of 1,5,9-cyclododecatriene were generated, such that the high concentration (67 ppm) chamber contained a mixture of aerosol and vapor components, while the low (10 ppm) and intermediate (25 ppm) concentration chambers contained primarily vapor, with little or no aerosol component. Exposure atmospheres were generated by metering the liquid test substance into a heated, glass, 3-neck mixing flask with an infusion pump. High pressure air was passed through the mixing flask and carried the test atmospheres to the exposure chamber. Dilution air was added between the flask and the chamber inlet for a total airflow of 60 L/min. Desired atmospheric concentrations of 1,5,9-cyclododecatriene were controlled by varying the test substance feed rate delivered to the mixing flask. The control group was exposed to air only. The atmospheric concentration of 1,5,9-cyclododecatriene was determined at approximate 60-minute intervals during each exposure by gas chromatography and gravimetric analyses for the vapor and aerosol components, respectively. Samples to determine particle size distribution were taken 3 times during the study from the 67 ppm chamber. Chamber temperature, humidity, oxygen concentration, and airflow were recorded.

Observations for morbidity and mortality were made daily. Body weights, food consumption, and individual clinical signs were recorded. Females were euthanized on Day 21G and the organs of the thoracic and abdominal cavities were examined for gross pathologic changes. The intact and empty uterine weights were recorded to calculate maternal body weight adjusted to exclude the products of conception. The corpora lutea count for each ovary of dams with viable fetuses was recorded. For each female with visible implants, the type (live and dead fetuses, and resorptions) and their relative positions were recorded. The uterus of each apparently "nonpregnant" rat was stained to detect very early resorptions. The body weight, sex, and external alterations for each fetus were recorded. For each litter, the first live fetus and every other live fetus thereafter were examined for visceral alterations. The heads of decapitated fetuses were fixed, examined, and alterations were recorded. The remaining fetuses were euthanized. Skeletal alterations were recorded for all live fetuses, excluding the fetal heads examined above.

GLP: Yes

Test Substance: 1,5,9-Cyclododecatriene, purity 99.83%

Results: The analytically determined mean concentrations of 1,5,9-cyclododecatriene were 10 ± 0.27, 25 ± 0.33, and 67 ± 1.9 ppm for the 10, 25, and 67 ppm exposure levels, respectively. The 1,5,9-cyclododecatriene aerosol generated in the 67 ppm chamber was considered to be respirable in rats. The mass median aerodynamic diameter (MMAD) measurement was 2.6 µm, with 13-56% of the particles less than 1 µm, 35-89% of the particles less than 3 µm, and 66-99% of the particles less than 10 µm. Chamber airflow, oxygen concentration, temperature, and humidity were 59-62 L/min, 21%, 22-27ºC, and 27-67% respectively.

Pregnancy ratios were 21/22, 20/22, 22/22, and 20/22 at 0, 10, 25, and 67 ppm, respectively. There were no mortalities or early deliveries observed at any dose level. A summary of other reproductive outcomes (means/litter) are provided in the table below:

Concentration (ppm)	0	10	25	67
Corpora Lutea:	15.6	15.4	14.8	15.0
Implantations:	14.1	14.1	13.3	13.8

Total No. of Resorptions:	1.0	0.7	0.4	0.7
Total No. of Fetuses:	13.1	13.4	13.0	13.1
Total No. of Live Fetuses:	13.1	13.4	13.0	13.1
Mean Fetal Weight (g):	5.68	5.63	5.55	4.93
Sex Ratio (male/female):	0.53	0.52	0.50	0.49

There were no compound-related effects on mean number of corpora lutea, implantations, resorptions, live fetuses, or fetal sex ratio at any exposure level. There was no evidence of compound-related embryolethality at any exposure level tested.

During the daily exposures, there was a diminished response to an alerting stimulus observed on 6 occasions in rats exposed to 67 ppm. There were no other significant clinical signs observed in this group or any other groups during the daily exposures.

No evidence of maternal or developmental toxicity was observed at 10 ppm. At 25 ppm, there was evidence of maternal toxicity, viewed as significant, compound-related reductions in maternal body weight, body weight change, and food consumption. Clinical observations (stained fur) were increased at this level as well. There was no other evidence of maternal toxicity, and there was no evidence of developmental toxicity at this level. Clear evidence of maternal and developmental toxicity was seen at 67 ppm. There were significant, compound-related reductions in maternal body weight, body weight change, and food consumption at this exposure level. Clinical observations (wet and/or stained fur) were increased at this level as well. There was no other evidence of maternal toxicity at this level. The only evidence of developmental toxicity was a significant reduction in mean fetal weight, and a concomitant increase in the incidence of delayed skeletal ossification.

Under the conditions of this study, maternal toxicity was observed at 25 and 67 ppm. The maternal no-observed-effect level (NOEL) was 10 ppm. Developmental toxicity was observed at 67 ppm. The developmental NOEL was 25 ppm. Therefore, the results of this study indicate that 1,5,9-cyclododecatriene is not likely to be uniquely toxic to

the rat conceptus.

Reference: DuPont Co. (1999). Unpublished Data, Haskell Laboratory Report No. DuPont-1559 (also cited in TSCA fiche OTS0557883-1).

Reliability: High because a scientifically defensible of guideline method was used.

Additional References for Developmental Toxicity: None Found.

5.4 Reproductive Toxicity:

Species/Strain: Rat/Crl:CD®(IGS)BR
Sex/Number: Male and female/10 per sex per dose group
Route of Administration: Gavage
Exposure Period: Males through test day 55
Females 4 weeks premating through 4-day lactation period
Frequency of Treatment: Daily
Exposure Levels: 0, 30, 100, 300 mg/kg
Method: OECD Guideline No. 422.

Details for the subchronic portion, including dosing scheme and toxicological parameters studied can be found in Section 5.2.

Following the 4-week premating period, each female was paired with a male of the same dosage group during a 1-2 week mating period. Measurements of body weight, food consumption, food efficiency, and clinical signs of toxicity in females were conducted weekly during gestation and on lactation days 0 and 4. At the end of an approximately 3-week post-mating period, surviving males and presumed nonpregnant females were sacrificed, and on lactation day 4, lactating females and offspring were sacrificed. Ten organs were weighed, and 40 tissues were preserved for microscopic examination. The testes, epididymides, ovaries, and gross lesions from all high-dose and control group rats were examined microscopically. All other preserved tissues from 5 male and 5 female rats, randomly selected from the high-dose and control groups were examined microscopically. Livers from 5 randomly selected female rats in the 30 and 100 mg/kg/day groups that delivered at least 1 live offspring were also examined microscopically. Offspring were weighed and evaluated for clinical abnormalities. Reproductive parameters recorded or calculated included gestation length, mating index, gestation

index, fecundity index, implantation site numbers, implantation efficiency, sex ratio, pups born alive, and viability index.

GLP: Yes

Test Substance: 1,5,9-Cyclododecatriene, purity 99.86%

Results: Results of the subchronic portion of the study, including effects on body weights, food consumption, clinical signs of toxicity, clinical chemistry, pathology/histopathology, and neurotoxicity can be found in Section 5.2. Results of reproductive performance are detailed below.

There were no test substance-related effects on reproductive parameters, which included gestation length, mating index, gestation index, fecundity index, implantation site numbers, implantation efficiency, sex ratio, pups born alive, and viability index. There any no changes in neurobehavioral parameters, or motor activity.

There were no test substance-related effects on clinical observations, number of pups born, number of pups born alive, or number of pups surviving through lactation day 4. Body weights of pups in the 300 mg/kg/day group were significantly decreased on lactation days 0 and 4.

A summary of reproductive outcomes are provided in the table below:

Dose (mg/kg)	0	30	100	300
Mating Index(%):	80.0	90.0	100.0	100.0
Fertility Index (%):	87.5	77.8	70.0	70.0
Gestation Length (days):	22.0	22.0	22.0	22.0
Implantations (mean/litter):	16.0	15.6	16.3	16.1
Implantation efficiency (%):	92.1	96.2	92.0	89.5
Gestation Index:	100.0	100.0	100.0	100.0
Mean % Born Alive:	98.3	99.1	99.2	99.0
0-4 Day Viability (%):	98.0	99.0	98.2	98.3

Sex Ratio (males):	0.45	0.50	0.49	0.45

The no-observed-adverse-effect level (NOAEL) was 100 mg/kg/day for males, 30 mg/kg/day for females, and 100 mg/kg/day for pups.

Reference: DuPont Co. (2000). Unpublished Data, Haskell Laboratory Report No. DuPont-3682.

Reliability: High because a scientifically defensible or guideline method was used.

Additional References for Reproductive Toxicity: None Found.

5.5 Genetic Toxicity

Type: ***In vitro*** **Bacterial Reverse Mutation Test**

Tester Strain: *Salmonella typhimurium* TA97a, TA98, TA100, TA1535 *Escherichia coli* strain WP2 *uvrA* (pKM101)

Exogenous Metabolic Activation: With and without Aroclor®-induced rat liver S9

Exposure Concentrations: 0, 10, 50, 100, 500, 1000, 2500, 5000 µg/plate

Method: The test substance was evaluated for mutagenic activity (1 trial) with and without exogenous metabolic (S9) activation. Three replicates were plated for each tester strain, test concentration, and condition. Dimethyl sulfoxide (DMSO) was used as the solvent and negative control. Positive indicators included the following: 2-aminoanthracene (2AA), 2-nitrofluorene (2NF), sodium azide (NAAZ), ICR 191 Acridine, and methyl methanesulfonate (MMS). Deionized water was the solvent for NAAZ, ICR 191 Acridine, and MMS. The solvent for the remaining positive indicators was DMSO. Solutions of the test substance were prepared immediately prior to treatment and were presumed to be stable under the conditions of the study. Treatment and control dosing solutions were not analyzed for concentration, uniformity, or stability.

Treatments with exogenous metabolic activation were conducted by adding 0.1 mL of negative control or test substance solution, 0.5 mL of S9 mix, and 0.1 mL of an overnight culture containing at least 1 x 10^8 bacteria to 2 mL agar. These components were mixed and poured onto a plate containing approximately 25 mL of Davis minimal agar with

dextrose (minimum agar plates). Treatments without activation were identical to those with activation, with the exception that the S9 mix was replaced with 0.5 mL of sterile phosphate buffered saline. Revertant colonies were counted after the individually labeled plates were incubated at approximately 37ºC for about 48 hours. When necessary, plates were refrigerated at approximately 2-4°C prior to counting. For each tester strain, the average number of revertants and the standard deviation at each concentration with and without S9 activation were calculated.

A test substance was classified as positive when the average number of revertants in any strain at any test substance concentration studied was at least 2 times greater than the average number of revertants in the negative control, and there was a positive dose-response relationship in that same strain. A test substance was classified as negative when there were no test substance concentrations with an average number of revertants that was at least 2 times greater than the average number of revertants in the negative control and there was no positive dose-response relationship.

GLP:	Yes
Test Substance:	1,5,9-Cyclododecatriene, purity 100%
Results:	Negative
Remarks:	No evidence of mutagenic activity was detected with or without metabolic activation.
Reference:	DuPont Co. (1996). Unpublished Data, Haskell Laboratory Report No. 585-96.
Reliability:	High because a scientifically defensible or guideline method was used.

Additional References for *In vitro* Bacterial Reverse Mutation Studies:

Data from these additional sources support the study results summarized above. These studies were not chosen for detailed summarization because the data were not substantially additive to the database.

Huels (1988). Unpublished Data, Report No. 88/004 (cited in IUCLID (1995). IUCLID Data Sheet "Cyclododeca-1,5,9-triene" (October 23)).

Shell Research Limited (1987). Unpublished Data, Report SBGR.87.175 (cited in IUCLID (1995). IUCLID Data Sheet "Cyclododeca-1,5,9-triene" (October 23)).

Type:	***In vitro* Clastogenicity Test**
Cell Type:	Human lymphocytes
Exogenous	With and without Aroclor®-induced rat liver S9

Metabolic Activation:	
Exposure Concentrations:	Trial 1: 0, 0.25, 0.5, 0.75, 1.0, 2.5 mg/mL Trial 2: 0, 0.5, 0.75, 1.0, 2.5, 3.5, 5.0 mg/mL Supplemental harvest from Trial 2: 1.0, 2.5, 3.5 mg/mL
Method:	The test substance was evaluated for clastogenic (chromosome-damaging) activity in human lymphocytes *in vitro* following 3-hour treatments with and without exogenous metabolic (S9) activation. The solvent (negative control) was acetone. For chromosome aberration trials, mitomycin C (MMC) and cyclophosphamide (CP), dissolved in water, were used as positive indicators for tests without activation and with activation, respectively. All dilutions of the test substance were prepared immediately prior to treatment of the cultures. Treatment and control dosing solutions were not analyzed for concentration, uniformity, or stability. Studies of cell proliferation, with and without S9 activation, were conducted to assess cytotoxicity. Cell cultures were treated with the test substance at concentrations of 0, 0.005, 0.01, 0.05, 0.1, 0.5, 1.0, and 5 mg/mL. Evaluation of the mitotic index (MI) was also used in determining cytotoxicity of the test substance. Approximately 48 hours after culture initiation, the medium was replaced with treatment medium. All test concentrations and solvent controls were evaluated in replicate cultures both with and without activation. After addition of the test or control substance, the cultures were incubated for approximately 3 hours at 37ºC. Following treatment, the cultures were rinsed, and fresh medium containing 5-bromodeoxyuridine (BrdU) was added. Incubation continued for approximately 24 hours, with Colcemid® present during the final 3 hours to arrest cells in metaphase. Cultures were handled under yellow filtered lights to avoid photolysis of BrdU-substituted DNA. Cells were harvested, fixed, and slides were prepared, stained, and coverslipped. Slides from the highest test concentration were compared with the solvent controls for evidence of cell-cycle delay. Successively lower concentrations were also scored for comparison. Where possible, 50 metaphase cells were scanned and scored as having gone through 1 (M1), 1-2 (M1+), 2 (M2), 2-3 (M2+), or 3 DNA replication cycles in the presence of BrdU. Cell-cycle delay was judged to be present where the proportion of slower-cycling cells (e.g.,

M1, M1+) was clearly increased relative to the control, and consequently the average generation time (AGT) was increased.

For the chromosome aberration trials, culture initiation, treatment, and cell harvests were conducted as described for the cytotoxicity assessment, except that BrdU was omitted from the medium, test concentrations and harvest times were adjusted as appropriate, positive indicators were included, and at least 2 independent trials were conducted. In both trials, metaphase cells were harvested approximately 19-21 hours after the end of treatment. In Trial 2, cells were also harvested approximately 43-45 hours after the end of the treatment (supplemental harvest) and evaluated. Well spread metaphases were evaluated for structural chromosome aberrations at 1000x magnification. For each trial with and without activation, 100 cells (50 from each replicate; 50 from male, 50 from female) were analyzed for each test level, the controls, and the positive indicator. Except for abnormal cells, only cells with 46 centromeres were scored. The aberrations observed were tabulated and categorized as chromatid- or chromosome-type aberrations. Gaps were also recorded.

The test substance was classified as clastogenic (positive) if the test substance produced a statistically significant increase in percent abnormal cells as compared to the negative control at one or more test concentrations and there was a statistically significant dose-related increase in percent of abnormal cells. The test substance was classified as nonclastogenic (negative) if the test substance did not produce a statistically significant increase in percent abnormal cells at any concentration tested and there was no statistically significant dose-related increase in percent abnormal cells.

GLP:	Yes
Test Substance:	1,5,9-Cyclododecatriene, purity 100%
Results:	Negative
Remarks:	In the cytotoxicity assessment, both with and without activation, the MI was decreased in a concentration-dependent manner. At 5 mg/mL, slides were unscorable in both sexes without activation, and MI was decreased to 26% of the negative control with activation. At 1 mg/mL, the MI was reduced to 38% of the negative control without metabolic activation, and 52% of the negative control with activation. In the activated system, at 5 mg/mL, AGT was

increased to approximately 23 hours as compared to 15 hours in negative controls. At 1 mg/mL, AGT was increased 18-19 hours with activation. Significant increases in AGT were not observed in the non-activated system.

Moderate cytotoxicity, as measured by a decrease in the MI, was observed with and without activation in Trial 1. The MI was reduced to 43% and 41% of the negative control in non-activated and activated systems, respectively, at 2.5 mg/mL in Trial 1. In Trial 2, the MI was reduced to 30% and 48% of the negative control in the non-activated and activated systems, respectively, at 5 mg/mL. No statistically significant increases in percent cells with structural chromosome aberrations were observed at any concentration tested. No dose-related increases in the percent of abnormal cells were observed in either activated or non-activated trials. There was no statistical increase in the percent of abnormal cells in the supplemental harvests. 1,5,9-Cyclododecatriene was not clastogenic in this assay.

Reference: DuPont Co. (1997). Unpublished Data, Haskell Laboratory Report No. 1997-00115.

Reliability: High because a scientifically defensible or guideline method was used.

Additional References for *In vitro* Clastogenicity Studies: None Found.

Type: ***In vivo* Rat Micronucleus Test**

Species/Strain: Rats/Crl:CD®(SD)BR

Sex/Number: Male/10 for the test substance, 5 for the negative control

Route of Administration: Inhalation

Concentrations: 0, 500 ppm (0, 3300 mg/m^3)

Method: Aerosol/vapor atmospheres of 1,5,9-cyclododecatriene were generated by metering the liquid test substance into a nebulizer. Filtered, houseline air introduced into the nebulizer atomized the liquid test substance and carried the resulting aerosol/vapor mixture through a glass cyclone elutriator and into a glass transfer tube. Dilution air added to the transfer tube carried the aerosol/vapor/air mixture into the top of the exposure chamber. The concentration of 1,5,9-cyclododecatriene was controlled by varying the amount of test substance delivered into the nebulizer. Exposure chambers were constructed of stainless steel and glass with a nominal internal volume of approximately 150 L. The atmospheric concentration of 1,5,9-cyclododecatriene was determined at approximately

60-minute intervals during each exposure by gas chromatography and gravimetric analysis for the vapor and aerosol components, respectively. One sample to determine particle size distribution (mass median aerodynamic diameter) was taken from the 500 ppm chamber during the study. Chamber airflow, temperature, relative humidity, and oxygen concentration were recorded.

Male rats (mean pre-treatment weight for rats evaluated for micronuclei was 231.4 g; 51 days old when exposed) were exposed nose-only to the test substance or negative control, respectively, for 6 hours per day for 2 consecutive days. Houseline air was the negative control, and the positive indicator was cyclophosphamide (CP). The test substance and positive indicator were assumed to be stable during the study. CP was administered to rats (52 days old) by oral intubation at 40 mg/kg.

Body weights and clinical signs were recorded. During exposure, all rats were observed for clinical signs of toxicity and for their reaction to an alerting stimulus. Immediately after sacrifice, marrow from 1 femur of each rat was collected. At least 3 slides per rat were prepared, fixed, and stained with acridine orange. Representative slides from each rat were examined blindly. Two thousand PCEs (polychromatic erythrocytes) per rat were evaluated for micronuclei. Cellular inclusions that were irregularly shaped or stained, or out of the focal plane of the cell were considered artifacts. The unit of scoring was the micronucleated cell; PCEs with more than one micronucleus were scored as a single MNPCE. Micronucleated NCEs seen in the optic fields scored to obtain 2000 PCEs were also counted. Additionally, the number of PCEs among 1000 erythrocytes was recorded for each rat.

GLP: Yes

Test Substance: 1,5,9-Cyclododecatriene, purity 100%

Results: Negative

Remarks: For each exposure, the mean aerosol concentration was added to the mean vapor concentration to calculate the total chamber atmospheric concentration of 1,5,9-cyclododecatriene. The analytically determined mean concentration in the exposure chamber targeted to 3300 mg/m^3 (500 ppm) was 3200 ± 280 mg/m^3 for the 2 exposures. The aerosol in the chamber was considered respirable in rats with a mass median aerodynamic diameter of 3.6 µm; 23% of the particles were less than 3 µm and

99% of the particles were less than 10 µm. The chamber airflow, temperature, relative humidity, and oxygen concentration were 35 L/min, 23-25ºC, 15-22%, and 21%, respectively.

There was no test substance-induced mortality during the study. Statistically significant body weight losses were observed in the test substance-treated and the positive indicator rats. No clinical signs of toxicity were evident in rats during exposure. Rats in the treatment group did, however, display responses to an alerting stimulus ranging from diminished to none. Test substance-related clinical signs observed in the treatment group after exposure included lethargy and/or irregular respiration, and likely represent manifestations of systemic toxicity.

There were no statistically significant increases in the MNPCE frequency in rats exposed to 1,5,9-cyclododecatriene. As expected, a statistically significant increase in MNPCE frequency was found in CP-treated rats. Additionally, no statistically significant depressions in the proportion of PCEs among 1000 erythrocytes were observed in rats exposed to the test substance.

Reference: DuPont Co. (1996). Unpublished Data, Haskell Laboratory Report No. 1028-96 (also cited in TSCA fiche OTS0558489-1).

Reliability: High because a scientifically defensible or guideline method was used.

Additional References for *In vivo* Studies: None Found.